Complete Summary

GUIDELINE TITLE

Management of type 2 diabetes mellitus.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Management of type 2 diabetes mellitus. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Nov. 70 p. [109 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Management of type 2 diabetes mellitus. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Nov. 80 p.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- "Prediabetes" (impaired fasting glucose or impaired glucose tolerance)
- Type 2 diabetes mellitus

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management

Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Internal Medicine
Nephrology
Neurology
Nutrition
Ophthalmology
Podiatry

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dietitians
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Podiatrists

GUIDELINE OBJECTIVE(S)

- To provide a comprehensive approach to the management of "prediabetes" (impaired fasting glucose or impaired glucose tolerance) and type 2 diabetes mellitus to include nutrition therapy, physical activity recommendations, pharmacologic therapy, self-management, as well as prevention and diagnosis of diabetes-associated complications and risk factors
- To decrease the percentage of patients with diabetes with poorly controlled blood sugars and cardiovascular risk factors (clinical strategies that target these high risk populations may be more viable with limited resources)
- To increase the percentage of patients with diabetes age 18-75 for whom recommended screening frequencies and ideal treatment goals are met
- To improve diabetes self-management skills

TARGET POPULATION

Adult patients age 18 and over with "prediabetes" or type 2 diabetes mellitus

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention

1. Laboratory tests including impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
2. Patient education including lifestyle behavior changes and cardiovascular risk reduction
3. Monitor and follow-up testing as indicated
4. Pharmacologic therapy including biguanides, alpha glucosidase inhibitors, angiotensin-converting enzyme (ACE) inhibitors and thiazolidinediones. (Note: None of these treatments have proven to be as effective as lifestyle change.)

Diagnosis

1. Detailed medical history, physical examination and confirmatory laboratory testing (refer to "Major Recommendations" section)

Treatment/Management

1. Pharmacologic therapy including:
    - Glycemic management
        - Individualized insulin therapy based on patient's lifestyle, treatment goals, and self-monitoring blood glucose (SMBG)
        - Oral agents: Sulfonylurea or metformin (first choice); Other oral agents, such as alpha glucosidase inhibitors, thiazolidinediones, meglitinides (short-acting secretagogues) if first choice not tolerated or contraindicated
        - Combinations of oral agents with other oral agents or insulin
    - Blood pressure control
        - Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)
    - Lipid Management
        - Statins
2. Self-management programs including:
    - nutrition therapy program
    - physical activity program (preceded by medical assessment of physical conditions, limitations, risk of cardiovascular disease, cardiac stress testing and blood glucose control)
3. Patient education for self-management, including disease process, prevention of complications, risk reduction, medication compliance, foot care and available community resources
4. Other measures to reduce cardiovascular risk: aspirin use, tobacco cessation
5. Ongoing assessment for complications; treatment and/or referral for complications as appropriate

MAJOR OUTCOMES CONSIDERED

Morbidity and mortality associated with type 2 diabetes mellitus and/or complications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine

its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary and a written response is prepared to address each of the responses received from member groups. Two members of the Committee on Evidence-Based Practice carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer and other practice systems. Evaluation and assessment occurs throughout the pilot test phase, which usually lasts for three-six months. At the end of the pilot test phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline; the Committee on Evidence-Based Practice reviews the revised guideline and approves it for release.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for the management of type 2 diabetes mellitus are presented in the form of 4 algorithms with a total of 30 components, accompanied by detailed annotations. Algorithms are provided for: Management of Type 2 Diabetes Mellitus, Glycemic Control, Blood Pressure Control, and Ongoing Management; clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III, Not Assignable) definitions are repeated at the end of the "Major Recommendations" field.

Clinical Highlights

1. Focus on cardiovascular risk reduction (blood pressure control, statin use, aspirin [ASA], and tobacco cessation). (Annotations #9).
2. Glycemic control of less than 7% often requires frequent drug intensification and use of combination therapy. (Annotations #9, 15, 17)).
3. Aggressive blood pressure control is just as important as glycemic control. Systolic blood pressure level should be the major factor for detection, evaluation, and treatment of hypertension. This may require the use of two or more agents (to include thiazide diuretics). (Annotations #9, 20-24) (see original guideline document for annotation #20).
4. Self-management support is necessary for people with diabetes to manage their disease. (Annotation #8)
5. Prevent microvascular complications through annual eye exams, foot risk assessments and foot care counseling, and annual screening for proteinuria. (Annotations # 27).

Management of Type 2 Diabetes Mellitus Algorithm Annotations

1. Diagnostic Testing for Diabetes or Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG)

   Patients presenting with symptoms of diabetes should be tested. Testing patients with hypertension, dyslipidemia, and heart disease is also recommended. Other patients at risk for diabetes are also appropriate for testing. (See the National Guideline Clearinghouse (NGC) summaries of the Institute for Clinical Systems Improvement (ICSI) guidelines: Hypertension Diagnosis and Treatment, Lipid Screening in Adults, the Preventive Services for Adults, and the Stable Coronary Artery Disease.)

   Evidence supporting this recommendation is of class: R

2. Evaluation of Patients with Elevated Glucose

   Evaluation may be completed in one or more visits over a reasonably short period of time. Clinical judgment is needed to determine the urgency of completing the evaluation.

   A. History

      For all patients:

      - Symptoms
      - Eating habits, weight history
      - Physical activity
      - Prior or current infections, particularly skin, foot, dental, and genitourinary
      - Symptoms and treatment of chronic complications associated with diabetes: eye, heart, kidney, nerve, sexual function, peripheral vascular, and cerebrovascular (these may be present at diagnosis)

- Current medications including over-the-counter (OTC) medications and alternative therapies
- Risk factors for atherosclerosis: smoking, hypertension, dyslipidemia, family history
- Family history of diabetes, cardiovascular disease, cerebrovascular disease, dyslipidemia
- Gestational history: delivery of an infant weighing more than 9 pounds, toxemia, stillbirth, or history of gestational diabetes
- Psychosocial and economic factors that might influence the management of diabetes
- Alcohol/drug use

For patients diagnosed with diabetes:

- Details of previous treatment programs, including diabetes education
- Current treatment of diabetes, including medications, nutrition, physical activity patterns and results of glucose monitoring
- Frequency, severity, and cause of acute complications such as hypoglycemia, hyperglycemia, and nonketotic hyperosmolar coma

Evidence supporting this recommendation is of class: R

B. Physical Examination
- Weight, height, body mass index (BMI), blood pressure
- Optic fundi
- Oral exam (dental and gingival health)
- Cardiovascular system: heart, peripheral circulation including pulses and bruits (abdominal, carotid, femoral)
- Skin: infections, xanthoma, insulin injection sites
- Feet: nails, web spaces, ulcers, pulses, calluses, structural deformities, protective sensation and shoes
- Neurological system: sensory state of hands and feet, muscle wasting, deep tendon reflexes
- Mental health assessment with consideration for depression/anxiety screen

Evidence supporting this recommendation is of class: R

C. Laboratory Evaluation
- Fasting plasma glucose or random plasma glucose
- Glycosylated hemoglobin (A_1, A_{1c}, glycated hemoglobin) (not required for impaired glucose tolerance [IGT]/impaired fasting glucose [IFG])*
- Fasting lipid profile: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides
- Serum creatinine
- Urine: ketones, glucose, protein, microalbuminuria, culture (if microscopic is abnormal or symptoms of infection present)**

* Glycosylated hemoglobin assays provide an accurate indication of long-term glycemic control. A1c is formed by the continuous nonenzymatic glycosylation of hemoglobin throughout the life span of an erythrocyte. This assay yields an accurate measure of time-averaged blood glucose during the previous six to eight weeks.

There are various methodologies (i.e. HbA, A1c, glycated hemoglobin) for this assay. At present, there are no established criteria for use as a diagnostic test. Clinically it can assist in determining duration and severity of hyperglycemia and can help guide treatment.

A1c is not influenced by food intake, physical activity or acute metabolic stress. The test can be done at any time of day and does not require fasting.

** Urine microalbumin tests can identify patients with early diabetic nephropathy when intervention may be most effective in delaying or preventing end stage renal disease (ESRD). Single tests for urinary microalbumin and urinary creatinine can accurately detect urinary microalbumin excretion. (For more information see Annotation #27, "Annual Assessment of Complications.")

Increased urinary microalbumin is a predictor of increased cardiovascular mortality.

Evidence supporting this recommendation is of classes: B, R

3. Diagnosis IGT/IFG (prediabetes)
    A. Diagnosis of Impaired Fasting Glucose (IFG)

        Fasting plasma glucose greater than or equal to 100 mg/dl and less than 126 mg/dl

    B. Diagnosis of Impaired Glucose Tolerance (IGT)

        Oral glucose tolerance test (OGTT) 2-hour plasma glucose: greater than or equal to 140 mg/dl and less than 200 mg/dl

4. Evidence supporting this recommendation is of class: R

4. Treatment of IGT/IFG (prediabetes)

Intensive lifestyle behavior change programs that include monitoring of regular physical activity recommendations and nutrition counseling can reduce the risk of type 2 diabetes in this population by about 50%. The following treatments are recommended for people with IGT or IFG:

- Intensive lifestyle behavioral change including a nutrition and activity plan by a registered dietitian, health educator, or other qualified health professional. Ongoing support of behavioral change is necessary.

- Cardiovascular risk reduction appropriate to the needs of the individual.
- Regular follow-up and reassessment of risks including rescreening for diabetes every 1-3 years.
- There is some evidence of prevention of diabetes through pharmacotherapy with biguanides, alpha glucosidase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, and thiazolidinediones. However, none of these treatments have proven to be as effective as lifestyle change.

Evidence supporting this recommendation is of classes: A, R

5. Diagnosis Type 2 Diabetes
    - Fasting plasma glucose greater than or equal to 126 mg/dl
    - Casual plasma glucose greater than or equal to 200 mg/dl plus typical symptoms of diabetes
    - In the absence of unequivocal hyperglycemia associated with acute metabolic decompensation, the results should be confirmed by repeat testing on a different day. At the present time A_{1c} should not be used to diagnose diabetes.

6. Needs Stabilization?

    Indications for immediate insulin treatment in type 2 diabetes mellitus*

    *Insulin therapy may not be permanent

    - Pregnancy - Oral agents do not have United States Food and Drug Administration (FDA) approval for use in pregnancy. The glucose goals are different in pregnancy and require more aggressive treatment. (Treatment of this condition extends beyond the scope of the original guideline document.)
    - Surgery, infection, steroids - If these conditions cause significant hyperglycemia, insulin may be most appropriate.
    - Severe symptoms, marked weight loss, and/or ketonuria with:
        - Glucose greater than 300 mg/dl fasting or
        - Random glucose over 350 mg/dl
    - Hyperosmolar, nonketotic state:
        - Glucose over 600 mg/dl, osmolality over 330 mosm/l
    - Inpatient care may be appropriate in the following situations:
        - Elderly patients with infection or illness, weight loss, dehydration, polyuria, or polydipsia
        - Life-threatening acute metabolic complications of diabetes (e.g., serum glucose >400 mg/dL, 300-400 mOsm/L, lactic acidosis, small to moderate amounts of ketones, serum pH <7.3, bicarbonate <15 mEq/L, anion gap >12)
        - Uncontrolled insulin-requiring diabetes during pregnancy.

7. Initial Stabilization for Outpatients Requiring Immediate Insulin Treatment

If the patient presents and is considered stable enough for outpatient care but meets indications noted above for starting insulin, there are several acceptable ways of initiating insulin.

- One example is to calculate the total daily dose of insulin at 0.3 units/kg and start bedtime glargine at 50% of the total dose, splitting the remaining 50% with short acting insulin before meals.
- Another example is to start an oral agent while simultaneously initiating glargine at a dose of approximately 0.1 units/kg.
- A third example is to calculate the total daily dose of insulin at 0.3 U/kg and use premixed insulin with 2/3 the dose in the a.m. and 1/3 in the p.m.

At presentation, all patients should be instructed on blood glucose monitoring; hypoglycemia recognition and treatment; and how/when to contact health care support. Patients should check blood sugars frequently when insulin is initiated. Patients should receive daily phone or visit contact for at least 3 days and have 24-hour emergency phone support if needed.

Patients should be referred for nutrition and diabetes education and be seen in a timely way after diagnosis, (e.g. within 1-7 days).

Insulin therapy may not be permanent, particularly if oral agents are added or if, at presentation, the patient is in metabolic stress (e.g. infections, acute metabolic complications, recent surgery, etc.). As the metabolic stress resolves, the insulin dose requirements may rapidly fall.

For the occasional unstable patient with type 2 diabetes, maximal doses of oral hypoglycemic agents may afford an approach to the patient who is psychologically resistant to or refuses insulin initiation.

Evidence supporting this recommendation is of classes: A, D

8. Recommend Self-Management Program
   A. Nutrition Therapy

      Medical nutrition therapy for diabetes emphasizes improving metabolic outcomes. Major goals are to attain and maintain in the normal or as close to normal range as is safely possible blood glucose, blood pressure, and lipid/lipoprotein levels. These goals help reduce the risk for chronic complications of diabetes and macro- and microvascular disease.

      Weight loss is also an important goal because it improves insulin-resistance, glycemic control, blood pressure and lipid profiles. Moderate weight loss (5% of body weight) can improve fasting blood glucose in many overweight or obese persons; however, those with longstanding disease may not be as responsive to weight loss. There is considerable interest in low-carbohydrate diets for weight loss, however, additional research is needed to determine the long-term

efficacy. (See the NGC summary of the ICSI guideline Prevention and Management of Obesity [Mature Adolescents and Adults]).

Appropriate nutrition therapy will be developed collaboratively with the person who has diabetes. Instruction may require a provider with expertise in medical nutrition therapy, and instruction may be obtained through individual or group consultation. It is important that physicians understand the general principles of medical nutrition therapy and support them for patients with diabetes. In most people, dietary recommendations are similar to those of the general population. Medical nutrition therapy is a Medicare Part B covered benefit.

1. Evaluate the patient's current eating habits and modify as needed. Recommend:
    - Setting goals and working together toward gradual, realistic lifestyle changes.
    - Healthful food choices: Foods containing carbohydrate from whole grains, fruits, vegetables and low fat dairy products should be included in a healthy eating plan.
    - Sucrose (e.g., table sugar) and sucrose-containing foods do not need to be restricted. However, they should be substituted for other carbohydrate sources, or if added, covered with insulin or other glucose-lowering medication. They should be eaten within the context of a healthy diet.
    - Reduce total caloric intake by moderating food/beverage and limiting total fat intake.
    - Because carbohydrate has the greatest impact on blood glucose, its effect can be minimized by the distribution of carbohydrates as evenly as possible throughout the day to smaller meals and snacks.
    - If one chooses to drink alcohol, and has not been cautioned against it, limit intake to one drink per day for women and two drinks per day for men, according to USDA guidelines. To reduce the risk of hypoglycemia, alcohol should be consumed with food.
    - In insulin-resistant individuals, reduced energy intake and modest weight loss improves insulin-resistance and glycemia in the short-term.
    - Avoid protein intakes of greater than 20% of total daily energy. The long-term effect of consuming more than 20% of energy as protein on the development of nephropathy has not been determined.

2. Select meal planning approach most comfortable for the patient, such as general or menu guidelines, simplified meal plan, exchanges and carbohydrate counting.
3. Individualize the nutrition prescription based on the nutrition assessment and treatment goals of each patient. For example, if the patient has been eating 45% of calories from fat, lowering fat to even 40% can be helpful.

Protein

a. 15% to 20% of the total calories
b. 0.8 to 1.0 g/kg if microalbuminuria is present; 0.8 g/kg if macroalbuminuria is present.

Carbohydrate

a. Total amount of carbohydrate is more important than the source and type of starch or sugar.
b. Added fructose as sweetening agent is not recommended as it may adversely affect plasma lipids. Naturally occurring fructose in fruits, vegetables, and other foods do not need to be avoided. The use of sugar alcohols, such as sorbitol or mannitol appear to be safe, however they may cause gastrointestinal side effects.
c. Non-nutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the FDA.
d. A variety of fiber-containing foods, such as whole grains, fruits, and vegetables have beneficial effects on hyperinsulinemia, lipids, and colon health. The large amounts of fiber needed to confer benefit may not be acceptable due to palatability and possible gastrointestinal side effects
e. Glycemic Index. Although carbohydrates do have differing glycemic responses, there is insufficient research to show that a low glycemic index diet establishes long-term glycemic benefit.

Fat

a. Patients with normal weight and lipids: similar to U.S. National Institutes of Health National Cholesterol Education Program guidelines (less than or equal to 30% calories from fat, less than 10% saturated fats and trans-saturated fatty acids, and less than 300 mg cholesterol). See the related National Guideline Clearinghouse (NGC) summary Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).
b. To lower LDL-cholesterol, energy derived from saturated fat can be reduced if weight loss is desired, or replaced with either carbohydrate or monounsaturated fat when weight loss is not a goal.
c. Weight control: balance lower fat and caloric consumption with regular physical activity of 30 minutes most days.
d. Patients with elevated cholesterol and LDL-cholesterol: implement NCEP-Therapeutic Lifestyle (TLC) Recommendations. TLC Diet: reduce saturated fat to

less than 7% calories, cholesterol less than 200 mg, consider increased soluble fiber intake (10-25 g/day) and plant stanols/sterols (2 g/day) and minimize trans-unsaturated fat intake.

e. The 2005 Dietary Guidelines for Americans recommend trans fat intake below 1% of calories. To illustrate this, a 2,000 calorie per day intake would translate into 20 calories per day from trans fats or about 2 g/day (there are 9 calories per gram of fat).
f. Patients with elevated triglycerides: improve blood glucose control, encourage weight loss, increase physical activity, avoid alcoholic beverages, moderate carbohydrate and add dietary saturated fat restriction.

Sodium

a. Medical nutrition therapy for hypertension control focuses on weight reduction and recommended sodium intakes of 1,500-2,400 mg per day. Additional recommendations include consuming five to nine servings of fruits and vegetables daily, and two to four daily servings of low-fat dairy products rich in calcium, magnesium, and potassium. Please refer to NGC summary of the ICSI guideline Hypertension Diagnosis and Treatment for additional information.

There is evidence that 10-20 lb weight loss may be a more reasonable expectation than recommending ideal body weights.

Evidence supporting this recommendation is of class: R

4. When usual measures to promote weight loss are unsuccessful in severely obese individuals with comorbidities, there may be a role for adjunctive pharmacotherapy or surgical procedures. Further research is being done in this area.
5. Provide for ongoing nutrition self-management and care.

Evidence supporting this recommendation is of classes: A, M, R

B. Physical Activity

The positive benefits of physical activity include: improved blood pressure values, improved lipid profile, improved cardiac status, increased insulin sensitivity, more effective weight management, and improved glycemic control, and helps in the management of depressive symptoms. Because the positive effects of increased physical activity diminish within days of the cessation of exercise, regular activity recommended.

Recent studies indicate that cumulative daily physical activity may be almost as beneficial as continuous physical exertion. The major

emphasis is to gradually increase level of physical activity either by increasing duration or frequency. Epidemiological studies suggest that regular aerobic physical activity is beneficial for the treatment of type 2 diabetes mellitus.

Evidence supporting this recommendation is of classes: A, C, R

Reinforce the ongoing need and benefits of physical activity at each visit, offering support and advice on ways to incorporate 30 minutes of physical activity into most days of the week.

1. Strategies for initiation of increased physical activity
    - Start by incorporating 10 minutes of increased activity into each day
        - Use stairs instead of elevator
        - Park car away from building entrance and walk
        - Walk to do errands
    - Overcome barriers
        - Self monitor activity performed using pedometer, time record, and/or journal
        - Be consistent
        - Have alternative activities for inclement weather
        - Find enjoyable activities
        - Be active at the time of day that is best for the individual
2. Medical evaluation to assess safety of exercise program
    - Assess physical condition and limitations of the patient
    - Assess for cardiovascular disease. Atypical symptoms and painless ischemia are more common in patients with diabetes.
    - Cardiac stress testing. Coronary disease is frequently silent in patients with type 2 diabetes. Standard treadmill exercise testing (TMET) may have decreased reliability, particularly in women. There are no studies that answer the questions about the value and frequency of stress testing. Stress testing is recommended in patients 35 years of age and older, those patients with a history of type 2 diabetes for 10 years or longer (type 1 greater than 15 years), patients with any additional risk factor(s) for coronary artery disease, and those patients with a history of microvascular disease, peripheral vascular disease, and autonomic neuropathy.
    - Assess blood glucose control
    - Assess knowledge of physical activity in relation to blood glucose control
    - When making a referral, make other health care providers aware of limitations for exercise
3. Physical activity can be intermittent or cumulative

    <u>Intermittent</u>

Frequency: 4 to 7 days/wk
Intensity: 55% to 69% predicted maximum heart rate
Time: Minimum of 8 to 10 minutes/session

Cumulative

Frequency: Physical activity every day (walking, taking stairs, housework, scheduled activity)
Intensity: Moderate activity (equivalent to brisk walk)
Time: Accumulate 30 minutes or more each day

C. Education for Self-Management

Adequate self-management support for patients requires integration of available self-management education and support resources into routine care. Usually appropriate education may require the expertise of the diabetes educator. This instruction can be obtained through individual or group consultation. Medicare reimbursement for diabetes self-management training requires this service be provided by an education program that has achieved recognition by the American Diabetes Association; the staff in such a program is multidisciplinary and includes at least a registered dietician (RD) and a registered nurse (RN) with experiential preparation in education and diabetes management. Cultural sensitivity is an important aspect of education for self-management. Providers should be aware of culturally appropriate community resources and provide support for persons with diabetes and their families to access community resources.

An education plan should be identified based on the needs of the individual and referral made to either an internal or external education resource. Periodic reassessment of educational goals is recommended.

Evidence supporting this recommendation is of classes: C, D, R

Components of self-management include:

- Describe the diabetes disease process and treatment options
- Goal setting to promote health, and problem solving for daily living
- Preventing, detecting and treating acute complications
- Preventing (through risk reduction behavior), detecting and treating chronic complications
- Self monitoring blood glucose, ketones (when appropriate), and using results to improve control
- Incorporate appropriate nutrition management
- Incorporate physical activity into lifestyle
- Utilizing medications (if applicable) for therapeutic effectiveness
- Awareness of culturally appropriate community resources/support for persons with diabetes mellitus and their families and ability to access community resources
- Integrating psychosocial adjustment to daily life

- Promote preconception care, counseling, and management during pregnancy, if applicable

D. Foot Care

Education should be tailored to patient's current knowledge, individual needs and risk factors. Patients should be aware of their risk factors and appropriate measures to avoid complications. (See Annotation # 27D, "Comprehensive Foot Examination with Risk Assessment" below.)

Evidence supporting this recommendation is of class: R

- Inspect feet daily for cuts, bruises, bleeding, redness and nail problems
- Wash feet daily and dry thoroughly including between the toes
- Do not soak feet unless specified by a health care provider
- Be careful of hot water
- Use of lotions, Vaseline, or creams is acceptable, but do not use between the toes
- Do not walk barefoot
- Check shoes each day for objects that may have fallen inside, excessive wear or areas that may cause irritation
- Avoid injuries from cutting toenails, avoid self-cutting calluses or corns
- Seek care immediately for new foot problems

E. Community Resources

There is some evidence for the effectiveness of community-based diabetes self-management education and support. These programs may complement the care and education that are routinely part of standard medical practice, and may enhance a patient's ability to self-manage their diabetes. The Task Force on Community Preventive Services, supported by the Centers for Disease Control and Prevention, recommends diabetes self-management education in community gathering places.

9. Set Individualized Treatment Goals

Key Points:

- The following goals are recommended: HbA_{1c} < 7%, getting patients on statins, BP < 130/80 mm Hg, ASA daily in patients $\geq$40 years of age, and avoidance of tobacco use.

The physician and patient must discuss and document the treatment goals and the plan to achieve the desired goals. Less strict goals may be established for the very elderly or for the patient with severe health problems (e.g., severe coronary artery disease, metastatic cancer, dementia). Control of hyperglycemia is important; however, in older persons with diabetes, a greater reduction in morbidity and mortality may result from control of

cardiovascular risk factors than from tight glycemic control. The following goals are recommended:

A. Goals for Glycemic Control - A_{1c} Less Than 7%

For patients with type 2 diabetes mellitus, the A_{1c} goal is <7%. [Conclusion Grade II: See Conclusion Grading Worksheet -- Appendix A -Annotation #9A (Goal for Glycemic Control) in the original guideline document]

Evidence supporting this recommendation is of classes: A, B, R

A_{1c} target levels should be individualized. Higher target levels may be appropriate in patients of an advanced age, those at higher than normal risk of hypoglycemia, and those with a limited life expectancy.

1. Biochemical Index

	Biochemical Index	Normal	Goal
Plasma Values	Average preprandial glucose	<100 mg/dl	90 to 130 mg/dl
	Average bedtime glucose	<120 mg/dl	110 to 150 mg/dl

The self monitoring blood glucose (SMBG) targets are based on plasma glucose values, which are 10% to 15% higher than whole blood glucose values. Most home blood glucose monitors are referenced to plasma levels. It is important that people with diabetes know whether their monitor and strips provide whole blood or plasma results. (Action suggested may depend on patient symptoms. For blood glucose levels less than 90 or 80, depend on individual patient considerations.)

Medical centers need to know what the standard is for A_{1c} and glycated hemoglobin in their labs and make the appropriate conversions.

2. Self-Monitoring Blood Glucose (SMBG)

Set frequency and timing of glucose monitoring. Examples include:

Therapy	Frequency and Timing
Nonpharmacologic or oral agent	Twice daily, rotate times, at least 2 to 3 days per week. Postprandial may be helpful.
Simple insulin regimens (1 or 2 shots daily)	Twice daily, rotate times, at least 3 to 4 days per week. Postprandial may be helpful.
Complex insulin regimens (3 or more shots daily)	Four or more times every day. Postprandial may be helpful.

Patients can monitor blood glucose in almost any setting and at any time. This can be used to guide therapy adjustments, to assess the impact of food or exercise on blood sugar, provide feedback, and document whether symptoms are related to hypoglycemia.

The major hazard associated with SMBG is the risk that inaccurate data may lead the patient or physician to inappropriate therapeutic decisions. Confirmation of unexpected results by obtaining a plasma glucose or repeating the test is recommended. Mean SMBG values not consistent with the glycosylated hemoglobin value suggest the SMBG is inaccurate.

Providers must review the results of SMBG at each office visit for diabetes. This reinforces the importance of SMBG, confirms the regular use of SMBG, and can be used to demonstrate or review with patients the relation of exercise and diet to glucose control.

Evidence supporting this recommendation is of class: R

B. Start Statin and Treat to Goal

Recent evidence and ATPIII consensus guidelines suggest that statins are beneficial for high-risk patients with a 10-year risk of cardiovascular event of > 20%, (e.g. CAD equivalency) even with baseline LDL of < 100. [Conclusion Grade: See Conclusion Grading Worksheet -- Appendix B -- Annotation #9B (Statin Use)]. Moderate to high dose statins and an LDL value of LDL < 70 is a therapeutic option for "very high-risk" patients. According to recent treatment trials, very high-risk patients would be those in the first years post MI.

Three pathways to improve lipids are: (1) medical nutrition therapy, (2) increase physical activity, (3) pharmacotherapy. Beneficial effects of statins on cardiovascular risk reduction may, in part, be

independent of their effects on lipids. Diabetes has been considered a coronary artery disease equivalent. Risk calculators for type 2 diabetes can be found at the following URL: http://www.dtu.ox.ac.uk/index.html?maindoc=/riskengine/download.html.

Seventy-five to eighty percent (75-80%) of adult patients with diabetes die of macrovascular disease-specifically coronary, carotid and/or peripheral vascular disease.

Dyslipidemia is a known risk factor for macrovascular disease.

Small density LDL-cholesterol (more atherogenic) particles are increased in type 2 diabetes, and LDL-cholesterol itself may differ in people with diabetes compared with people without diabetes. Patients with diabetes develop more atherosclerosis than patients without diabetes with the same quantitative lipoprotein profiles. In individuals with elevation in triglycerides, a statin can reduce major vascular events.

High triglycerides and low HDL-cholesterol are independent risk factors for cardiovascular disease in the patient with diabetes. Individuals with elevated triglycerides have significant cardiovascular risk reduction with the use of fibrates. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix B -- Annotation #9B (Statin Use)]. While a number of studies support favorable changes in lipid profiles with niacin alone, randomized controlled trials considering hard cardiovascular outcomes are lacking.

Evidence supporting this recommendation is of classes: A, C, R

C. Goals for Blood Pressure (BP) Control - BP Less Than 130/80 mm/Hg - Emphasis on Systolic BP Control

In type 2 diabetes, insulin resistance may cause hypertension by increasing sympathetic activity, renal reabsorption of sodium or vascular tone.

Uncontrolled hypertension is a major cardiovascular risk factor that also accelerates the progression of diabetic nephropathy. When hypertension is identified, it should be aggressively treated to achieve a target blood pressure of less than 130/80 mm Hg. See the Blood Pressure Control algorithm below.

For patients with type 2 diabetes mellitus, the systolic blood pressure goal is < 130 and the diastolic blood pressure goal is < 80. [Conclusion Grade II: See Conclusion Grading Worksheet -- Appendix C -- Annotations #9C, 21, 23 (Goals for BP) in the original guideline document].

Evidence supporting this recommendation is of classes: A, R

D. Aspirin (ASA) / Antiplatelet Medication Unless Contraindicated

Patients with type 2 diabetes are at a significantly high risk for development of heart disease. For patients with type 2 diabetes mellitus, initiate low-dose aspirin therapy (81 to 325 mg daily) in patients 40 and older unless there is a contraindication to aspirin therapy. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix D -- Annotation #9D (Aspirin Use) in the original guideline document].

Evidence supporting this recommendation is of classes: A, B

If aspirin is contraindicated, consider use of clopidogrel (Plavix®) or ticlopidine (Ticlid®). For more information, please refer to the NGC summary of the ICSI guideline Stable Coronary Artery Disease.

E. Goals for Tobacco Use - Smoking Cessation, if Indicated

Avoid tobacco use. See the related NGC summary of the ICSI guideline Tobacco Use Prevention and Cessation for Adults and Mature Adolescents.

10. Are Treatment Goals Met?

Major long-term goals of care in type 2 diabetes are cardiovascular disease prevention (see the related Blood Pressure Control algorithm) and achieving optimal glycemic control.

Setting initial goals that are achievable, however modest they may be, may encourage patients to take further steps along the way to the more ambitious long-term goals.

Goals and progress towards agreed upon goals should be briefly reviewed at each office visit for diabetes. Adjustment of goals will likely be required over time, and patient involvement in this process can increase levels of patient involvement in care, give patients a greater sense of control of their diabetes, and allow flexibility in management of diabetes during periods of high stress or major life transitions.

11. Treatment Goals Not Met
    A. Modify treatment based on appropriate related guidelines (e.g., Hypertension Diagnosis and Treatment; Lipid Management in Adults; Tobacco Use Prevention and Cessation for Adults and Mature Adolescents; Major Depression In Adults For Mental Health Care) and/or:
    B. See the Glycemic Control and Blood Pressure Control algorithms and/or:
    C. Consider Referral to Diabetes Care Team or Specialists

Diabetes Care Team

Consultation with a diabetes educator is suggested if the patient is having difficulty adhering to a nutrition and exercise regimen and the patient is having difficulty adhering to, or accurately completing blood glucose monitoring or may need answers to some questions.

Every primary care physician must develop a relationship with a diabetes education program to provide other options for management. The American Diabetes Association (ADA) publishes a list of recognized educational programs in each state. These programs may be staffed with endocrinologists or primary care providers plus diabetes educators including dietitians, nurses, and other health care providers who are Certified Diabetes Educators (CDE) or have didactic and experiential expertise in diabetes care and education.

Eye Care Specialist

A dilated eye examination for diabetic eye disease should be performed annually in patients with type 2 diabetes mellitus.

DQIP and HEDIS measures allow for biennial screening of low-risk patients defined as having two out of three of the following criteria:

- Not on insulin therapy
- A1c less than 7%
- Dilated eye exam documenting no retinopathy during year prior

The ADA continues to recommend annual screening.

Evidence supporting this recommendation is of class: R

Endocrinologist/Nephrologist

Consultation with a specialist is suggested if persistent proteinuria, worsening microalbuminuria and elevation in serum creatinine or blood urea nitrogen, or hypertension unresponsive to treatment is seen. For additional discussion, see Annotation #28, "Nephropathy".

Endocrinologist/Neurologist

Consultation with a specialist is suggested if neuropathy progresses and becomes disabling.

Endocrinologist/Cardiologist/Hypertension Specialist

Consultation with a specialist is suggested if blood pressure is refractory to treatment; the patient has marked associated postural hypotension, or symptoms of coronary artery disease.

Foot Care Specialist

Consultation with a specialist is suggested if the patient is unable to care properly for his/her own feet, needs prescriptive footwear and/or more serious problems such as foot deformities (e.g., Charcot deformity), infected lesions, and ulcers, deformed nails, or thick calluses are present.

D. Assess Patient Adherence

Nonadherence with medications can limit the success of therapy and help to explain why a patient is not achieving treatment goals. To screen for nonadherence, clinicians can ask patients open-ended, nonthreatening questions at each office visit. The assessment should include probes for factors that can contribute to nonadherence (fear of adverse reactions, misunderstanding of chronic disease treatment, depression, cognitive impairment, complex dosing regimens, or financial constraints.)

1. Assess the patient's knowledge of his/her condition and his/her expectations for treatment
2. Assess the patient's medication administration process
3. Assess the patient's barriers to adherence

Interventions to enhance medication adherence should be directed at risk factors or causes of non-adherence. Interventions may include simplifying the medication regimen, using reminder systems, involving family or caregivers in care, involving multiple disciplines in team care, providing written and verbal medication instructions, setting collaborative goals with patients, and providing education about medications (including potential adverse effects) and about diabetes in general.

Evidence supporting this recommendation is of class R

E. Evaluate for Depression

There is a substantial increase in the prevalence of depression among people with diabetes as compared to the general adult population. The prevalence of depression is two times as likely in people with diabetes and without complications, and depressive symptoms may be found in up to 50% of those who have diabetes with complications. Depression impacts the ability of a person with diabetes to achieve blood glucose control, which in turn impacts the rate of development of diabetes complications.

Identification and management of depression is an important aspect of diabetes care. Intervention studies have demonstrated that when depression is treated, both quality of life and glycemic control improve. Counseling may be effective, especially among those who are having difficulty adjusting to the diagnosis of diabetes or are having difficulty living with diabetes. Pharmacotherapy for depression is also effective. The ICSI Major Depression in Adults For Mental Health Care guideline provides more detailed suggestions for the management of depression.

Evidence supporting this recommendation is of classes: M, R

Glycemic Control Algorithm Annotations

12. Glycemic Control Algorithm

Medical nutrition therapy may be all that is required to treat diabetes, especially for the patient with early mild symptomatic disease. Medical nutrition therapy should be maintained throughout the course of the disease, even as pharmacologic agents are used. Oral agent medications are generally used if medical nutrition therapy alone does not succeed in obtaining patients' goals within a reasonable time frame, usually no longer than 2 to 3 months.

At the time of diagnosis, if patients have severe symptomatic disease, insulin should be initiated. With appropriate educational support and care, the risks of insulin may not differ from many oral agents. In some circumstances when glucose intolerance is significant and the patient is unwilling to consider insulin or it is not felt to be appropriate, the initiation of combinations of oral agents can be appropriate. Insulin is indicated when there is a failure to achieve treatment goals with oral agents.

It is important to remember that patients can move both ways on the Glycemic Control algorithm, (e.g., they can move off of specific pharmacologic therapies as lifestyle changes are made that improve glycemic control). Diabetes is a progressive disease, however, and the use of pharmacologic agents will likely become necessary in the majority of patients, even if they are able to follow through with nutrition and physical activity recommendations.

Evidence supporting this recommendation is of class: A

13. Pharmacologic Agent(s) - Which is Best?

Key Points:

- Age and weight of the patient, as well as presence of renal dysfunction, cardiopulmonary comorbidities and hepatic disease must be considered when choosing pharmacologic agents.

Annotations #14 and 15 will address specific medications and the treatment of hyperglycemia. Only general guidelines can be given when deciding about which pharmacologic agent will be best for a specific patient. While each patient presents with unique circumstances, the following clinical circumstances should be considered:

A. Age of patient

It is important to recognize that risks of medications are often increased with advancing age, but this does not justify the withholding of medications that may reduce the symptoms of polyuria, nocturia,

and frequent visits to the bathroom that may place the patient at risk of hip fracture or falls.

With age, decline in renal function is often not reflected in a measurable change in serum creatinine because of an accompanying decline in muscle mass. Because of this, metformin should be used with caution in elderly patients.

Decline in ventricular function and risks for volume overload can be occult in the elderly and may become clinically apparent with the use of thiazolidinediones.

In select circumstances, because of the risks of hypoglycemia, variable diet habits and renal clearance and function, it may be safer to consider initial low dose short-acting sulfonylurea (e.g., glipizide or repaglinide/nateglinide when a meal is eaten).

B. Weight of the patient

Type 2 diabetes is often associated with obesity which may be key to significant insulin resistance and the metabolic syndrome.

Metformin, which is more often associated with weight loss or maintenance, is preferred. Because of significant insulin resistance associated with obesity, metformin and thiazolidinediones which improve insulin action have been used. The data for long-term use of thiazolidinediones, and their safety versus efficacy is not available.

C. Renal dysfunction

Renal dysfunction increases the risk for hypoglycemia in particular with the use of oral hypoglycemic agents.

Metformin and Alpha glucosidase inhibitors should not be used.

Thiazolidinediones may be considered, but the potential risks of fluid retention need to be considered.

Short-acting oral agents glipizide, glimepiride (in which serum levels have been noted to decrease in mild renal failure), repaglinide, or nateglinide may be preferred if an oral agent is felt to be necessary in the face of renal dysfunction.

Insulin may be the safest when serum creatinine is greater than 1.8 mg or creatinine clearance is less than 60 cc/min.

D. Cardiopulmonary Comorbidities

Obstructive sleep apnea, chronic hypoxia, class III or IV heart failure increase the risks of lactic acidosis.

Metformin should not be used.

Patients started on thiazolidinediones should be instructed to report signs of lower extremity swelling, rapid weight gain, and shortness of breath.

Short acting sulfonylurea (e.g., glipizide), repaglinide/nateglinide, the cautious use of longer acting oral agents or insulin may be safest.

E. Hepatic Disease

Hepatic disease or insufficiency increases the risks of lactic acidosis and hypoglycemia and influences the metabolism of many oral agent medications.

Metformin and thiazolidinediones should not be used if alanine aminotransferase (ALT) is 2.5 to 3 times upper limits of normal (ULN).

First generation sulfonylureas, glipizide, and glyburide have some component of hepatic metabolism and should be used with caution because of the risks of hypoglycemia.

Insulin would be considered safest.

14. Prescribe Insulin Therapy

- Insulin programs should be individualized based on the patient's lifestyle, treatment goals, and self-monitoring blood glucose (SMBG). Many patients can be taught to interpret SMBG results and adjust insulin doses.

  Evidence supporting this recommendation is of class: R

- Human insulin is now the only available insulin in the United States.
- Total dose ranges from 5 units/day to several hundred units/day.
- Average insulin doses are 0.6 to 0.8 units/kg of body weight per day.
- Obese patients may require more than 100 units/day.
- Meal times and snacks must be consistent. Synchronize insulin with food intake patterns.
- The time course of action of insulin preparations is presented in the original guideline document.
- Lispro (Humalog) and Aspart (Novolog) insulin should not be taken more then 15 minutes before meals in contrast to regular insulin which should ideally be taken at least 30 minutes before a meal to better match the insulin peak action with post-meal hyperglycemia.
- Patients who are testing their blood glucose before meals and adjusting insulin doses to match meals may find Lispro or Aspart insulin to be more effective although generally studies have not shown an improvement in A_{1c} when compared to regular insulin taken according to package insert (30 to 45 minutes preprandial).

- Effective use of Lispro or Aspart insulin may require adjustment of the basal intermediate or long-acting insulin and more frequent doses of basal insulin.
- Glargine should not be mixed with other insulins, diluted with other solutions, or given intravenously.
- Glargine insulin is most often used subcutaneously once daily at bedtime.
- Insulin pump therapy may be helpful for patients who are interested in more intensified management of blood sugars and want more flexibility, or if pregnancy is desired. Candidates for pump therapy should be evaluated by an endocrinologist or diabetes specialist to assess patient understanding, self-care knowledge including medical nutrition therapy, responsibility and commitment. Insulin pump therapy is more commonly used in type 1 patients, but is also being used by some type 2 patients.

15. Prescribe Oral Agent(s)/Titrate to Goal

Please consult the manufacturer's product labeling insert for full prescribing information.

The single best choice drug for oral agent therapy for type 2 diabetes has not been determined. The United Kingdom Prospective Diabetes Study (UKPDS) provides strong evidence that metformin may offer advantages in monotherapy for obese patients with type 2 diabetes. Sulfonylureas are also a good choice for monotherapy, are inexpensive and generally well tolerated. Additionally, the UKPDS did not find any adverse effect of sulfonylureas on long-term outcomes. The maximum clinically effective dose of any individual drug is often lower than the maximum allowable dose per day.

1. Second Generation Sulfonylureas

   (See the original guideline document for specific dosage recommendations.)

   Efficacy

   - The A_{1c} lowering commonly achieved with sulfonylureas is 1.5-2.0%.
   - The dose should be increased every 1 to 2 weeks until satisfactory glycemic control or the maximum dose is reached.
   - There are no major differences in sulfonylureas on effectiveness in controlling hyperglycemia. Switching from one to another is rarely beneficial in improving hyperglycemia.

   Safety

   - These agents are contraindicated in diabetic ketoacidosis and in patients with known hypersensitivity to sulfonylureas.
   - There are rare cross-sensitivities for patients with sulfa allergies.

- These agents should be used with caution in patients with hepatic or renal disease.
- Glipizide may be relatively safer than glyburide in patients with mild renal impairment.
- Hypoglycemia risk increases with impaired renal function. Glimepiride may cause less hypoglycemia in these circumstances.
- Glyburide has the highest rate of hypoglycemia of the sulfonylureas listed.

2. Metformin

   (See the original guideline document for specific dosage recommendations.)

   Efficacy

   - The A_{1c} lowering commonly achieved with metformin is 1.5% to 2.0%.
   - Absorption and bioavailability of Glucophage XR 2000 mg once daily is similar to that of metformin 1000 mg twice daily. Costs favor the use of metformin for patients who can manage twice a day dosing.
   - The major effect may be reducing hepatic glucose production.
   - Metformin is indicated for treatment of type 2 diabetes as monotherapy or in combination with sulfonylureas or insulin.

   Safety

   - Metformin is contraindicated in patients with known hypersensitivity, renal disease, congestive heart failure (treated with medications), acute or chronic metabolic acidosis (including diabetic ketoacidosis).
   - Do not use metformin in renal disease (creatinine greater than or equal to 1.5 mg/dl in men; creatinine greater than or equal to 1.4 mg/dl in women) because of possible lactic acidosis. In patients over age 80, check a creatinine clearance and use with caution. Even temporary reductions in renal function (e.g., pyelography or angiography) can cause lactic acidosis.
   - Do not use in patients with chronic obstructive pulmonary disease, severe hepatic disease or alcoholism.
   - Side effects may be transient and can include metallic taste, diarrhea, nausea, and anorexia.
   - The use of metformin in pregnancy or lactation is not recommended.
   - As monotherapy, metformin does not cause hypoglycemia.

3. Alpha glucosidase inhibitors

   (See the original guideline document for specific dosage recommendations.)

Efficacy

- The A_{1c} lowering commonly achieved with alpha glucosidase inhibitors is 0.5% to 1%.
- These agents are most appropriate in patients with glucose and glycosylated hemoglobin only moderately above goal.
- These agents delay carbohydrate absorption, which reduces postprandial blood glucose and insulin levels.
- These agents must be taken at the beginning of a meal to be effective.
- These agents are indicated for treatment of type 2 diabetes as monotherapy and as combination therapy (miglitol with sulfonylureas; acarbose with sulphonylureas, metformin or insulin).

Safety

- These agents are contraindicated in patients with known hypersensitivity, serum creatinine levels greater than 2 mg/dl, abnormal baseline liver function tests, and inflammatory bowel disease.
- Absorbed metabolites of acarbose may rarely cause elevated transaminase. Monitor aspartate transaminase (AST) every 3 months for 1 year.
- Side effects may include abdominal cramping, flatulence, and diarrhea. Tolerance develops, so start with low dose and increase gradually.
- As monotherapy, these agents do not cause hypoglycemia.

4. Thiazolidinediones

(See the original guideline document for specific dosage recommendations.)

Efficacy

- The A_{1c} lowering commonly achieved with thiazolidinediones is 1.0% to 1.5%.
- Thiazolidinediones (TZDs) improve insulin action in peripheral tissues, particularly muscle.
- Both pioglitazone and rosiglitazone are indicated for combination therapy with sulfonylureas, metformin or insulin.
- Both LDL and HDL cholesterol concentrations may increase slightly

Safety

- TZDs are contraindicated in patients with known hypersensitivity. Their use in pregnancy and lactation is not recommended.

- TZDs, alone or in combination with other antidiabetic agents, including insulin, can cause fluid retention, which may lead to heart failure. Do not use in patients with moderate to severe heart failure (New York Heart Association Class III and IV cardiac status).
- Side effects may include moderate weight gain, edema and mild anemia, all due at least in part, to fluid retention.
- As monotherapy,TZDs do not cause hypoglycemia.
- Measure ALT at baseline and periodically thereafter
- Administration of gemfibrozil increases plasma levels of rosiglitazone. Decreases in the dose of rosiglitazone may be needed when gemfibrozil is added.

5. Meglitinides (short-acting secretagogues)

   (See the original guideline document for specific dosage recommendations.)

   Efficacy

   - The average A_{1c} lowering commonly achieved is 0.5%.
   - The mechanism of action of these agents is to stimulate insulin secretion (similar to sulfonylureas).
   - These agents have a short duration of action, 1-4 hours.
   - These agents are usually taken 15 min before meals (range of 0 to 30 min)
   - These agents are indicated for use in combination with metformin or TZDs.

   Safety

   - The major side effect of these agents is hypoglycemia but the incidence may be less common than with sulfonylureas.
   - Skip the dose if the meal is not eaten.
   - Doses of nateglinide should be adjusted for hepatic impairment.
   - Administration of gemfibrozil significantly increases repaglinide blood levels, which may lead to hypoglycemia. Avoid concomitant use of gemfibrozil and repaglinide.

6. Combination products

   (See the original guideline document for specific dosage recommendations.)

   The UKPDS study shows good evidence for prescribing metformin in obese type 2 patients as a first choice. Metformin is the only pharmacologic agent that has shown decreased overall mortality in patients with diabetes.

   Evidence supporting this recommendation is of class: A

Head to head trials on rosiglitazone and pioglitazone have not been done to date, and would be necessary to determine which drug is more efficacious in decreasing A_{1c} and in cholesterol changes.

Evidence supporting this recommendation is of classes: A, R

17. Additional Agents

Key Points:

- Because type 2 diabetes is a progressive disease, combination medications are often needed to achieve goals.

Combination medications: Because type 2 diabetes is a progressive disease, combination medications are often needed. Degree of poor glycemic control and expectations for response of each agent (often 0.5% to 2% decrease in A_{1c} per agent) influence the timing and choice of combinations. Logical combinations are listed in the original guideline document.

Evidence supporting this recommendation is of class: A

19. Insulin Alone or Insulin + Oral Agent(s)

If treatment goals are not met on oral agents, or if oral agents are contraindicated, then it is necessary to begin insulin either alone or as an adjunct to oral therapy. There are many regimens that have been studied and are efficacious. Some commonly used regimens are discussed in the original guideline document.

Evidence supporting this recommendation is of class: A, R

Blood Pressure Control Algorithm Annotations

20. Blood Pressure Control Algorithm

Control of BP is at least as important as glycemic control for people with diabetes.

Evidence supporting this recommendation is of class: A

21. Is Systolic Blood Pressure Equal to or Greater Than 130 mm/Hg?

For patients with Type 2 Diabetes Mellitus, the systolic blood pressure (BP) goal is <130 and the diastolic blood pressure (BP) goal is <80. [Conclusion Grade II: See Conclusion Grading Worksheet - Appendix C - Annotation #9C, 21, 23 (goals for BP) in the original guideline document].

Evidence supporting this recommendation is of class: A, B, R

A report from the UKPDS showed an inverse relationship between systolic blood pressure and the aggregate end point for any complication related to diabetes. The lowest risk occurred at a systolic blood pressure below 120 mmHg. The ABCD trial achieved a blood pressure of 132/78 in the intensive therapy group and had a lower mortality rate (5.5% vs. 10.7%), but there were no statistically significant differences in cardiovascular events to account for the mortality difference.

The goal for patients with renal insufficiency and urinary protein excretion greater than 1 to 2 g/day should be less than 120/75.

22. Treat Systolic Blood Pressure to <130 mm/Hg. While Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers (ARBs) are Preferred First Line Therapy, Two or More Agents (to Include Thiazide Diuretics) May Be Required

    For patients with type 2 diabetes mellitus, ACE inhibitors or ARBs can reduce progression of micro- and macrovascular complications. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix E -- Annotations #22, 34A (Treatment with ACE Inhibitors or ARBs) in the original guideline document].

    While ACE inhibitors and ARBs are preferred first-line therapy, two or more agents (to include thiazide diuretics) may be required. For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix F - Annotations #22, 34D (Thiazide Diuretics) in the original guideline document].

    Nonpharmacologic and pharmacologic methods are recommended at blood pressures greater than 130/80 mm/Hg. The initial focus of treatment should be the systolic blood pressure.

    Treatment of isolated systolic hypertension, as well as combined systolic and diastolic hypertension, in both young and elderly people protects against major cardiovascular diseases. Drug treatment should be initiated if systolic BP is greater than or equal to 130 mm Hg. ACE inhibitors are the first choice of antihypertensive in people with diabetes if not contraindicated. The possible advantages to ACE inhibitors include renal protection, decreased insulin resistance, lack of adverse effect on lipids, and decreased CV risk reduction.

    In the UKPDS population atenolol and captopril had similar effectiveness on lowering blood pressure and preventing complications. Beta-blockers have additional beneficial effects in patients with known coronary artery disease. Previous data has shown that beta- blockers worsen glucose tolerance and lipid profiles and may mask the symptoms and prolong recovery from hypoglycemia and worsen peripheral vascular disease. Diuretics transiently and modestly increase LDL-cholesterol and triglycerides but do not affect HDL-cholesterol. The adverse lipid effects of these medications may be accentuated in patients with a preexisting dyslipidemia. Thiazide and loop diuretics may worsen glucose tolerance in direct proportion to the degree of hypokalemia that they induce. Preventing or minimizing hypokalemia reduces

the hyperglycemia. A low-sodium diet is therefore essential to the effective use of diuretics in patients with diabetes. Despite these potential concerns, the ALLHAT study and other long-term hypertension treatment trials demonstrate a reduction of CHD events when diuretics are used. For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure.

Evidence supporting this recommendation is of classes: A, D, R

23. Is Diastolic Blood Pressure <80 mm/Hg?

Key Points:

- For patients with type 2 diabetes mellitus, the systolic blood pressure goal is <130 and the diastolic blood pressure goal is <80.

The Hypertension Optimal Treatment (HOT) trial provides evidence that a target diastolic blood pressure less than 80 mm Hg has a cardioprotective effect in people with diabetes. This study reported that in the diabetic subgroup (n=1,501) major cardiovascular events were reduced by > 51% (p=0.005) in those randomized to a diastolic BP goal of < 80 mm Hg compared to < 90 mm Hg. The HOT study has been criticized by some because this was a post hoc analysis of a subgroup of patients in the study and the number of events is relatively small. Nevertheless, results are consistent with UKPDS. UKPDS achieved an average diastolic blood pressure of 82 in the tightly controlled group (vs. 87 mm Hg in the less tightly controlled group). The more tightly controlled group had diabetes related end points reduced by 24% (p=0.005) and death by 32% (p=.019).

For patients with type 2 diabetes mellitus, the systolic blood pressure (BP) goal is <130 and the diastolic blood pressure (BP) goal is <80. [Conclusion Grade II: See Conclusion Grading Worksheet -- Appendix C - Annotations #9C, 21, 23 (Goals for BP) in the original guideline document].

Evidence supporting this recommendation is of class: A

24. Treat Diastolic Blood Pressure to <80 mm Hg

Combinations of medications are often required to achieve goals. Thirty percent of patients in the tight blood pressure arm of the UKPDS with goal less than 150/85 mm Hg required 3 or more antihypertensive medications to achieve the mean 144/82 mm Hg. Findings from the ALLHAT study suggest that thiazide diuretics be considered as part of a multi-drug regimen.

Evidence supporting this recommendation is of classes: A, M

Ongoing Management Algorithm Annotations

25. Ongoing Management and Follow-Up of People with Diabetes

- Frequency of visits depends on blood glucose control, changes in the treatment regimen, and presence of complications of diabetes or other medical conditions.
- Patients starting or having a major change in their treatment program (such as initiating insulin therapy) may need to be in contact with their care provider as often as daily until glucose control is achieved, the risk of hypoglycemia is low, and the patient is competent to conduct the treatment program.
- Contact with the patient after a major modification of the treatment plan (such as introducing a new medication) should not be delayed greater than 1 week.
- Regular visits should be scheduled for insulin-treated patients at least quarterly and for other patients at least semiannually. More frequent visits may be necessary if treatment goals are not achieved.
- Cardiovascular disease is the primary cause of morbidity and mortality in people with type 2 diabetes. The risk of coronary artery disease is approximately doubled in men and quadrupled in women with diabetes.

In studies of general population groups coronary artery disease deaths have been substantially reduced by the treatment of hypertension, hypercholesterolemia and smoking. Lipid treatment has also been shown to be of benefit in diabetes. Therefore, risk factor reduction is prudent for patients with diabetes. Data also support the daily use of aspirin as a method to reduce cardiovascular events in patients with diabetes. See Annotation #9b, "Start Statin and Treat to Goal" and the Blood Pressure Control algorithm.

Evidence supporting this recommendation is of classes: A, R

26. Maintain Treatment Goals
    - Nutrition/Physical Activity: Work with individual patients regularly to set realistic goals.
    - Monitor A_{1c} every 3 to 6 months. In insulin treated patients and non-insulin-treated patients with poor metabolic control, quarterly A_{1c} may assist management.
    - Monitor lipid profile yearly (cholesterol triglycerides, HDL and LDL cholesterol). Treat to achieve recommended goals. (See Annotation #9b, "Start Statin and Treat to Goal"). If lipid goals are consistently met, patient is in metabolic control, has stable clinical conditions, and has not had a change in medication, an annual lipid profile is not mandatory. Diabetes is a major risk factor for coronary artery disease, and many patients with diabetes also have lipid disorders. Thus, control of dyslipidemia in diabetes is important because evidence shows that correcting lipid disorders reduces the rate of coronary artery disease events.
    - Monitor blood pressure each visit and control hypertension to recommended levels. See the Blood Pressure Control algorithm.
    - Ask about aspirin (ASA) use and recommend aspirin use in patients over 40 unless contraindicated.
    - Ask about alcohol and tobacco use and assist with cessation if indicated.

27. Annual Assessment of Complications

A. Targeted Annual History and Physical Exam

1. The history should assess:

- Results of self monitoring blood glucose; validate results at least once a year (i.e., check patient's glucose meter against an office random capillary glucose)
- Adjustments by the patient of the therapeutic regimen
- Frequency, causes, and severity of both hyperglycemia and hypoglycemia
- Problems with adherence to therapeutic regimen
- Symptoms suggesting development or progression of the complications of diabetes
- Current medications; over-the-counter (OTC) medications, and alternative therapies
- Documentation of eye care specialist exam results
- Alcohol/drug use patterns
- Lab assessment of liver function (LFT) and/or creatinine to assess ongoing acceptability of medication usage

2. The targeted physical exam should assess:

- Weight
- Blood pressure
- Cardiovascular - evaluation of preexisting problems
- Feet (nails, web spaces, calluses, ulcers, structural deformities, protective sensation and shoes)

B. Specialist Dilated Eye Exam

C. Renal Assessment

See Annotation Appendix B, "Treatment of Diabetic Nephropathy," in the original guideline document.

Urinary albumin excretion should be tested annually by a microalbuminuria method. If albuminuria is above normal, serum creatinine should be measured. Some factors can artifactually increase the levels of albumin in the urine and should be avoided at the time of the urine collection; these factors include: blood in the urine, prolonged heavy exercise, fever, congestive heart failure, uncontrolled diabetes, severe hypertension, urinary tract infection (UTI) and vaginal fluid contamination of specimen.

If the dipstick or urine analysis test is negative for protein, then a more sensitive early screening test is indicated. A qualitative urinary microalbumin screen (e.g., Micral®) can be used to detect urinary microalbumin. If qualitative is positive, a quantitative test must be performed. Another option is a timed collection of urine (24 hr. or overnight), but this is not always necessary with the availability of the microalbumin creatinine ratio test. A microalbumin screening test should be done each year on patients with type 2 diabetes. If positive (exceeds 30 mg/g), it should be repeated twice in the next 3 months. If 2 out of 3 of these screening microalbuminuria tests are positive,

the individual has microalbuminuria and interventions should be considered. A negative finding should be followed yearly; a positive finding should be followed periodically to see if the interventions are effective in diminishing the albuminuria.

Evidence supporting this recommendation is of class: R

D. Comprehensive Foot Exam With Risk Assessment

Patients with one or more risk factors for foot complications should be educated about their risk factors and appropriate measures taken to avoid complications. Measures may include self-management education, more intensive follow-up, and/or referral to appropriate specialist.

Evidence supporting this recommendation is of class: R

Risk factors for foot complications include:

- Loss of protective sensation (inability to appreciate a 5.07 Semmes-Weinstein monofilament at one or more sites on the plantar toes or metatarsal heads) (see Annotation Appendix A, "Using a Semmes-Weinstein Monofilament to Screen the Diabetic Foot for Peripheral Sensory Neuropathy" in the original guideline document)
- Peripheral vascular disease (absent pedal pulse, history of claudication or ischemic skin changes)
- Structural deformities (bunion, hammertoes, Charcot deformity, limited joint mobility or prior amputation)
- Skin disorders (nail deformity, callus, fissure, tinea or ulceration)
- Footwear (excessively worn, ill fitting or inappropriate shoes)

E. Cardiovascular and Cerebrovascular Complication Assessment
- History of cardiovascular symptoms such as chest pain, vascular claudication, transient ischemic attack (TIA)
- Cardiac and carotid exams
- Evaluate cardiovascular status before advising increased intensity of exercise

Evidence supporting this recommendation is of classes: A, B, R

F. Special Considerations
- Influenza vaccine every year
- Pneumococcal vaccine - consider repeating the immunization for those at risk of losing immunity after five years including:
    - Nephrotic syndrome
    - Chronic renal disease
    - Other immunocompromised states
- There is evidence that ACE inhibitors are beneficial in reducing cardiovascular morbidity and mortality in acute myocardial

infarction (MI), congestive heart failure (CHF), and type 2 diabetes patients at high risk for cardiovascular disease and in improving renal outcomes in diabetes. Results of the HOPE (Heart Outcomes Prevention Evaluation) study strongly support the use of ACE inhibitors for patients with diabetes who are at high risk for cardiovascular disease. In the Second Australian National Blood Pressure Study (ANBP2), the use of ACE inhibitors in older patients was associated with better cardiovascular outcomes despite similar reductions in blood pressure from diuretics. Confirming studies would be helpful to strengthen this recommendation or to generalize recommendations to all patients with diabetes.

- Vitamin E has no apparent effect on cardiovascular outcomes.

Evidence supporting this recommendation is of class: A

28. Treatment and Referral for Complications
    A. Nephropathy: In an examination of diabetes complications in ethnically diverse populations with uniform medical coverage, ethnic minorities have an elevated incidence of end-stage renal disease (ESRD).

       In type 2 diabetes, albuminuria may be present at the time of diagnosis in about 10 percent of patients, and another 10 percent later develop it. Progression to renal failure is less certain in type 2 patients than in type 1 patients, and appears to be modulated by genetic and other factors. Patients with clinical nephropathy almost always have retinopathy and coronary artery disease.

       Numerous interventions are appropriate at different stages of renal function in order to prevent or slow the progression of renal disease and associated cardiovascular disease.

       1. Glucose Control - Improved glucose control at any stage of renal function reduces renal disease progression. See the Glycemic Control algorithm.
       2. ACE Inhibitors and ARBs have been shown to slow the progression of microalbuminuria to clinical proteinuria and to slow the progression of overt nephropathy to ESRD. These agents appear effective even in normotensive microalbuminuric individuals. This class of drugs must not be used in pregnancy. Within one week of initiation, check for elevations in potassium and creatinine levels and monitor for cough.

          For patients with type 2 diabetes mellitus, ACE inhibitors or ARBs can reduce progression of micro- and macrovascular complications. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix E - Annotations #22, 28A (Treatment with ACE inhibitors or ARBs) in the original guideline document].

3. Hypertension Control - Although ACE inhibitors and ARBs seem to have special renal protective properties beyond their antihypertensive effect, any effort to optimize blood pressure will help the kidneys. When significant microalbumin or overt nephropathy is present there may be a tendency to retain sodium. In this case, a loop diuretic added to the antihypertensive regimen is often helpful. A few studies show certain calcium channel blockers reduce microalbuminuria. A goal BP of 130/80 is recommended. See the Blood Pressure Control algorithm.
4. CV Risk Factor Intervention - Dyslipidemia is often present with microalbuminuria and should be treated aggressively. Dyslipidemia may be an independent risk factor for progression of renal disease. Smoking is associated with the onset and progression of microalbuminuria.
5. Restriction of dietary protein has been shown to slow progression of overt nephropathy (macroalbuminuria), and there may be some benefit in dietary protein reduction in microalbuminuric patients. In these circumstances, protein intake should be reduced to the adult RDA of 0.8-1.0 g/kg body weight per day with microalbuminuria present, and 0.8 gm/kg body weight per day with macroalbuminuria present.

Treatment for microalbuminuria includes aggressive blood pressure control, glycemic control, ACE inhibitor or ARB use and aggressive cardiovascular risk factor screening and management. Strongly consider referral to nephrology any patients with a creatinine greater than 1.5 mg, or nephrotic range proteinuria (greater than 3 g/24 hr). Nephrology interventions often include early patient education as renal disease progresses, review and reinforcement of the medical regimen, and preservation of arm veins for future vascular access. Patients with a creatinine clearance of less than 30 ml/min should be referred to nephrology for discussions of future options and to enhance the ability to receive a future transplant. These patients also have significant enough renal impairment that they also benefit from more intensive nutritional interventions and proper management of anemia and bone disease. See the Blood Pressure Control algorithm.

Evidence supporting this recommendation is of classes: A, B, R

B. Neuropathy: Peripheral neuropathy is difficult to prevent and treat. Most patients with type 2 diabetes and peripheral neuropathy have few symptoms but are found on examination to have diminished reflexes and sensation. Sometimes neuropathy can be very painful, especially at night, with "pins-and-needles" numbness and tingling in a stocking-and-glove

distribution. Absence of reflexes or decreased thermal, vibratory, proprioceptive or pain sensation may be noted on examination and confirm the diagnosis. Good glycemic control should be the first control to symptomatic neuropathy. Treatment with amitriptyline, nortriptyline, or trazodone in doses beginning at 25 mg at night and increasing to 75 mg may help some patients. Topical treatment with capsaicin, 0.025% cream three to four times per day, has also shown benefit. Carbamazepine and gabapentin may improve neuropathic pain also. These medications may provide symptomatic relief, but they do not improve the neuropathy.

Evidence supporting this recommendation is of class: R

C. Retinopathy: Prevalence of retinopathy is related to the duration of diabetes mellitus. After 20 years of diabetes mellitus more than 60% pf patients with type 2 diabetes have some degree of retinopathy. Diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults ages 20 to 74 years.

Up to 21% of patients with type 2 diabetes mellitus are found to have retinopathy at the time of diagnosis of diabetes mellitus. Generally retinopathy progresses from mild background abnormalities to preproliferative retinopathy to proliferative retinopathy.

Poor glucose control is associated with progression of retinopathy. High blood pressure is a risk factor for the development of macular edema and is associated with the development of proliferative retinopathy. See the Glycemic Control and Blood Pressure Control algorithms.

Screening for diabetic retinopathy saves vision at a relatively low cost. In fact, screening costs may be less than the costs of disability payments for those that go blind. Laser photocoagulation surgery is effective in preventing visual loss in diabetic retinopathy.

Studies have shown that the retinal examination by physicians who are not eye care specialists are not reliable in detecting retinopathy.

Evidence supporting this recommendation is of classes: A, C, R

Treatment includes glycemic and blood pressure control. Periodic screening and dilated eye exams by an eye specialist and early treatment of diabetic retinopathy prevents visual loss. See the Glycemic Control and Blood Pressure Control algorithms.

D. Cardiovascular and Cerebrovascular disease: Treatment includes control of cardiovascular risk factors (hypertension, hyperlipidemia and smoking cessation) and aspirin use. Patients with coronary artery disease (CAD) may be treated medically or surgically. Consider referring patients with known CAD to cardiology and patients with known carotid disease to surgery. Congestive heart failure (CHF) is also common in patients with diabetes. Caution should be used when prescribing spironolactone and eplerenone to people with diabetes, especially in combination with angiotensin-converting enzyme inhibitors. Close monitoring of potassium and renal function is necessary. See the Blood Pressure Control algorithm. For patients with type 2 diabetes mellitus, thiazide diuretics in the treatment of hypertension can reduce cardiovascular events, particularly heart failure. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix F - Annotations #22, 28D (Thiazide Diuretics) in the original guideline documents].

Evidence supporting this recommendation is of class: A

Advanced coronary artery disease may be treated medically or surgically. However, some studies suggest that coronary artery bypass grafting (CABG) may be less effective in older patients with diabetes than in other groups, perhaps because of microvascular disease in the coronary circulation, but most likely due to the extensive nature of diffuse disease with difficulty in bypassing the number of lesions present. One study found better survival in people with diabetes with CABG than with PTCA.

Patients with type 2 diabetes have twice the average risk of suffering a stroke. It is unsure whether good glycemic control reduces this risk. However, treatment of hypertension, smoking and hyperlipidemia reduces the risk of stroke in most persons. See Annotation #9, "Set Individualized Treatment Goals" and the Blood Pressure Control algorithm.

E. Peripheral vascular disease: Peripheral arterial disease is commonly associated with diabetes. As many as 36% of patients with diabetes have lower-extremity peripheral arterial disease based on lower-extremity blood pressure readings. However, a typical history of intermittent claudication or an absent peripheral pulse is less commonly noted.

Peripheral vascular disease in combination with peripheral neuropathy places patient with diabetes at increased risk for amputations of the lower extremity. Peripheral vascular disease may be slowed by smoking cessation and treatment of hypertension and dyslipidemia. (See Annotation #9b, "Start Statin and Treat to Goal" and the Blood Pressure Control algorithm). Aggressive daily foot care, inspection of the feet at every office visit, early treatment of foot infections, treatment

of callus, use of moisturizing lotion and proper footwear may forestall problems, including amputation. Vascular surgery may also prevent amputation in some patients with established severe peripheral vascular disease.

Treatment includes glycemic, blood pressure and lipid control, as well as smoking cessation, which may slow the progression. Proper high-risk foot management is necessary to prevent ulceration and amputation. Consider referral of patients with claudication and/or absent pedal pulses to surgery. Vascular surgery may prevent amputation in some patients with severe peripheral vascular disease. See the Glycemic Control and Blood Pressure Control algorithms.

Definitions:

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

Four detailed and annotated clinical algorithms are provided for:

- Management of Type 2 Diabetes Mellitus
- Glycemic Control

- Blood Pressure Control
- Ongoing Management

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithms are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., goal for glycemic control; goal for LDL level; goals for blood pressure, aspirin use and treatment with angiotensin converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective medical management of "prediabetes" (impaired fasting glucose or impaired glucose tolerance) and type 2 diabetes mellitus through a comprehensive approach that includes nutrition therapy, physical activity recommendations, pharmacologic therapy, self-management, as well as prevention and diagnosis of diabetes-associated complications and risk factors.

POTENTIAL HARMS

- The action of insulin preparations is highly variable among individuals, with values varying depending on the site and depth of injection, skin temperature and exercise.
- Oral insulin agents do not have U.S. Food and Drug Administration (FDA) approval for use in pregnancy.
- Glargine should not be mixed with other insulins, diluted with other solutions, or given intravenously.
- With second generation sulfonylureas, there are rare cross-sensitivities for patients with sulfa allergies. These agents should be used with caution in patients with hepatic or renal failure. Hypoglycemia risk increases with impaired renal function. Glyburide has the highest rate of hypoglycemia of all the sulphonylureas.
- Metformin may have unpleasant side effects such as metallic taste, diarrhea, nausea, and anorexia. These may be transient. Use with caution in elderly. The use of metformin in pregnancy or lactation is not recommended.

- Abdominal cramping, flatulence, and diarrhea are common side effects of alpha glucosidase inhibitors. Tolerance may develop. Absorbed drug metabolites of acarbose may rarely cause elevated transaminase.
- Thiazolidinediones, alone or in combination with other antidiabetic agents including insulin, can cause fluid retention, which may lead to heart failure. Side effects may include moderate weight gain, edema and mild anemia, all due, at least in part, to fluid retention. The use of agents is not recommended in pregnancy and lactation. Both low-density lipoprotein and high-density lipoprotein cholesterol concentrations may increase slightly.
- Hypoglycemia is the major side effect of meglitinides (short-acting secretagogues). There have been case reports of severe hypoglycemia in patients taking repaglinide (Prandin) concurrently with gemfibrozil (Lopid).
- Caution should be used when prescribing spironolactone and eplerenone to people with diabetes, especially in combination with angiotensin-converting enzyme (ACE) inhibitors.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to Sulfonylureas

- Diabetic ketoacidosis
- Hypersensitivity to sulphonylureas

Contraindications to Metformin

- Hypersensitivity, acute or chronic metabolic acidosis (including diabetic ketoacidosis).
- Renal disease (creatinine $\geq$1.5 mg/dl in men, $\geq$ 1.4 mg/dl in women)
- Chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF treated with medication), severe hepatic disease, or alcoholism.

Contraindications to Alpha Glucosidase Inhibitors

- Serum creatinine levels greater than 2 mg/dl
- Abnormal baseline liver function tests
- Inflammatory bowel disease
- Hypersensitivity

Contraindications to Thiazolidinediones

- Hypersensitivity
- Moderate to severe heart failure (New York Heart Association [NYHA] Class III and IV cardiac status)

Contraindications to Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers (ARBs)

- Pregnancy

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for release, a member group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

Recommended Educational Resources

The guideline work group has provided recommended website resources for practitioners and the public. Refer to the original guideline document.

IMPLEMENTATION TOOLS

Clinical Algorithm
Quality Measures
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED NQMC MEASURES

- Management of type 2 diabetes mellitus: percentage of adult patients with diabetes with A1c less than 7%.
- Management of type 2 diabetes mellitus: frequency of low-density lipoprotein (LDL) cholesterol values in adult patients with diabetes by category: less than 100 mg/dL, 100 to 130, greater than 130, incalculable, untested.
- Management of type 2 diabetes mellitus: percentage of patients who have had a screen for A1c in the past six months, an annual low-density lipoprotein (LDL) test, A1c value less than 7%, LDL less than 100, blood pressure less than 130/80, who don't use tobacco and are regularly using aspirin.
- Management of type 2 diabetes mellitus: percentage of patients with diabetes mellitus with A1c measured in the last 6 months.
- Management of type 2 diabetes mellitus: percentage of patients with diabetes with microalbumin tested within the last 12 months.
- Management of type 2 diabetes mellitus: percentage of patients with diabetes with eye exam documented within last 12 months.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Management of type 2 diabetes mellitus. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Nov. 70 p. [109 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 Mar (revised 2004 Nov)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Committee on Evidence-Based Practice

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline. Readers of the guideline may assume that only work group members listed below have potential conflict of interest to disclose.

No work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Management of type 2 diabetes mellitus. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Nov. 80 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ICSI pocket guidelines. April 2004 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2004. 404 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 30, 1999. The information was verified by the guideline developer on August 4, 1999. This summary was updated by ECRI on October 13, 2000 and May 7, 2002. The summary was most recently updated on March 14, 2003. The updated information was verified by the guideline developer on May 15, 2003. This summary was updated again by ECRI on July 8, 2004 and January 25, 2005.

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